

## THE BARE ESSENTIALS



# Multiple sclerosis

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Multiple sclerosis (MS) is caused by inflammatory demyelination and axonal loss in the central nervous system (CNS) (brain and spinal cord). The key characteristics of the scarring ("sclerosis") and its clinical sequelae are "dissemination in space", affecting different anatomical sites, and "dissemination in time", appearing episodically over time.

## EPIDEMIOLOGY

### Prevalence and incidence

In the UK, the prevalence is about 120/100 000 population and the annual incidence is 7/100 000 population. This means the average general practitioner may never be involved in the diagnosis of MS in their career but will have 2–4 MS patients on their list, of which 1–3 will be significantly disabled. Depending on how care is organised, up to 20% of a neurologist's general follow-up clinic may be made up of people with MS.

### Gender, age and race

- ▶ A typical patient, at the time of diagnosis, is a white woman in her 20s.
- ▶ Multiple sclerosis is three times more common in women than men, a ratio that has increased over the last century for unknown reasons.
- ▶ It usually starts in young adults—onset before puberty or after the age of 50 is rare.
- ▶ The disease is most common in White populations, especially in Northern countries.
- ▶ It is seen less frequently in Asians, except offspring of migrants who have settled in the West.
- ▶ It is occasionally encountered in the British Afro-Caribbean.
- ▶ It is very rare among the indigenous peoples of Africa and Australasia.

## THE PHASES OF MULTIPLE SCLEROSIS

The natural history of three types of MS is shown in fig 1.

**Relapse** is a clinically evident "attack" of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks, and then gradually resolving, completely or partially. Different symptoms of a relapse may appear at different times: by convention, any appearing within 30 days of the first symptom are said to be part of the same relapse. Strictly speaking, the first episode of demyelination

cannot be called a "relapse", but is termed an "episode". 80% of cases start in this way. The risk of a relapse is doubled after viral infection or major life events.

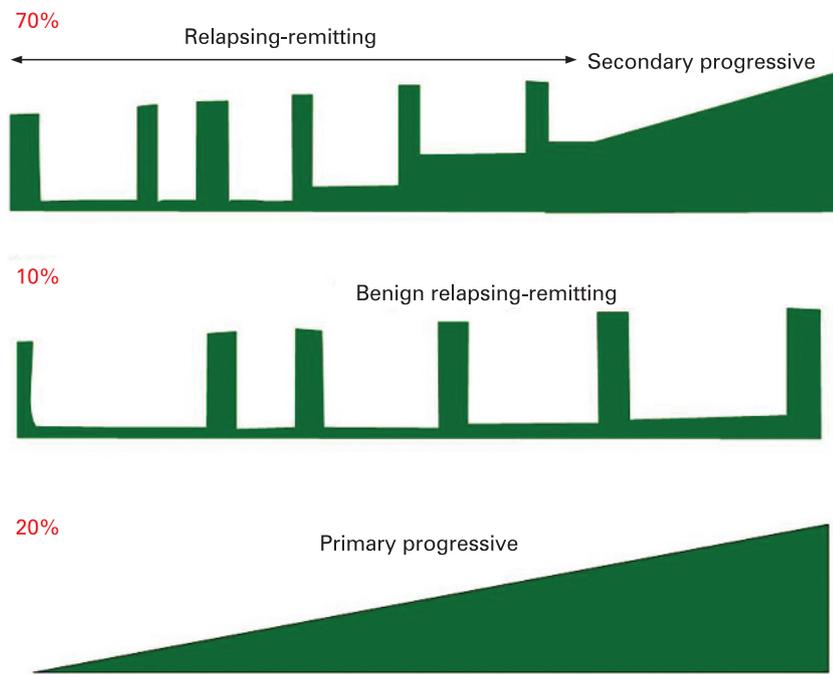
**Clinically isolated syndrome of demyelination** is a single clinically evident episode of demyelination in the brain or spinal cord without any preceding episodes. This is not (yet) "MS" because there has not yet been multiple attacks to give dissemination in time or space.

**Conversion from clinically isolated syndrome to relapsing-remitting multiple sclerosis.** Over time, most people with a clinically isolated syndrome have a subsequent relapse, so fulfilling the clinical criteria for relapsing-remitting MS (see below). The presenting brain MR scan helps to prognosticate: if it shows any white-matter lesions, the chance of a relapse is 50% over the subsequent 2 years, increasing to 80% at 20 years (which means of course that conversely 20% of patients with abnormal scans will not go on to develop MS). If the presenting scan is normal, the risk of a relapse over the next 20 years is only 20%.

**Relapsing-remitting MS** is defined as more than one clinical attack of demyelination, that is an initial episode followed by at least one relapse, separated by period(s) of complete or partial recovery, termed "remission(s)". The initial relapse rate is usually less than 1/year, and subsequently declines. With time, recovery from each episode is incomplete and fixed disability accumulates. Some 10% of all patients have "**benign MS**", which is characterised by lack of significant disability even after 20 years of clinically evident disease. This is by definition a retrospective diagnosis and of questionable value as many such patients do subsequently develop disability.

**Conversion from relapsing-remitting to secondary progressive MS.** The risk of entering the progressive phase increases with clinically evident disease duration (25% at 10 years from onset, 50% within 20 years and 75% after 35 years). It usually starts at around 40 years of age.

**Secondary progressive MS.** Symptoms are continuous and gradually worsen, without remission. Superimposed relapses may occur, but at much lower frequency than in the relapsing-remitting phase. In practice, it is only really possible to diagnose the onset of secondary progression in retrospect and after at least 12 months of observation.



**Figure 1** The natural history of the three types of multiple sclerosis. Horizontal axis is time passing, vertical axis is “disability”.

**Primary progressive MS.** 20% people with MS experience continuous worsening from disease onset with no preceding relapses, although relapses may subsequently occur, at low frequency.

### DIAGNOSING MS

The traditional clinical diagnosis of MS requires two or more episodes, at least 30 days apart, of symptoms attributable to demyelination at different sites in the CNS, ie dissemination in time and space. The McDonald criteria (see box) endorse these criteria, but also allow information from MR scans to be incorporated into the diagnosis. These criteria are complex and designed to standardise research; their use in everyday clinical practice varies between countries and centres. In a classic study by McAlpine in 1972, initial symptoms of MS were weakness in one or more limbs in 35%, optic neuritis 20%, paraesthesiae 20%, diplopia 10%, and disturbance of micturition 5%.

### History

- ▶ Symptoms characteristic of demyelination are: Lhermitte’s symptom (“an electric shock/tingle runs down my back/legs when I bend my head forward”), which may also occur with vitamin B12 deficiency, radiation myelopathy or rarely cervical cord compression, and the Uhthoff phenomenon (“my symptoms reappear/worsen when I have been for a run/had a hot bath/got cross”).
- ▶ When people with MS describe their sensory symptoms they often use complex imagery

(“like hot water trickling down my face”) rather than “numbness” or “pins and needles”.

- ▶ It is important to ask about past symptoms, especially problems with vision, walking and balance. These may be perfectly straightforward examples of demyelination, which were passed off as a virus or a mystery illness (“I lost vision in one eye when I was in my twenties ... I was paralysed for two weeks and then got better”). Alternatively, episodes may have been misdiagnosed as other medical conditions, eg “labyrinthitis”, “repetitive strain injury”, “Bell’s palsy”, “cystitis”.
- ▶ Note current level of mobility; it is very hard to judge progression without some baseline statement about disability.
- ▶ Fatigue is the sense of overwhelming difficulty of doing tasks (physical or cognitive) that are relatively easy at other times of day, or at first execution. It is more drawn out than the fatigability of myasthenia and does not lead to sleepiness, but to exhaustion and the need for rest. It may occur on its own (and accusations of “making it up”) early in the disease course, or in combination with other symptoms.
- ▶ Family history and any contact with people affected by MS is useful to know early on to help counselling and anticipate expectations. In MS, there is a 20% chance another family member may be affected; autosomal dominant or mitochondrial patterns of inheritance are red flags (see differential diagnosis).

### Examination

- ▶ The most common physical signs in unselected groups of patients with MS are impaired visual acuity (more common than impaired colour vision) and an extensor plantar response.
- ▶ Almost pathognomonic of MS are an internuclear ophthalmologia or a relative afferent pupillary defect.
- ▶ It is very unusual to have had MS for a decade and no impairment of vibration sensation in the feet.
- ▶ A hard sensory level is rare; just like sensory symptoms, sensory signs are usually complicated and difficult to delineate (and often not worth bothering with in detail).
- ▶ Absent reflexes and wasting are red flags that the diagnosis of MS may be incorrect (although a cord plaque at the dorsal root entry zone may abolish the root level reflex, and disuse atrophy may occur in very disabled MS patients).
- ▶ Never hang a diagnosis on a “pale disc”, especially “temporal pallor” which is a particularly soft sign.
- ▶ It is very unusual (1% cases) for people with MS to be registered partially sighted. However, women with Leber’s hereditary optic neuropathy may develop an MS-like illness.

### The McDonald criteria for diagnosing multiple sclerosis

The McDonald criteria endorse the clinical diagnosis of MS (two or more episodes, at least 30 days apart, of symptoms attributable to demyelination at different sites in the CNS) but also allow the incorporation of MRI evidence into the criteria for dissemination in time and space.

**Dissemination in time** For those with a clinically isolated syndrome of demyelination, MS may be diagnosed in the absence of further clinical attacks if (i) an MR brain scan, at least 3 months later, shows one or more gadolinium-enhancing lesions or (ii) two scans are done, the first at least 30 days after onset of the clinical event and the second at least 30 days again after that, and one or more new T2 lesions are found on the second scan.

**Dissemination in space.** If there have been several clinical episodes at the same neurological site, MRI lesions at other locations demonstrate dissemination in space.

The formal criteria, hard to remember and never used in routine practice, are at least three features from:

- ▶ one gadolinium-enhancing lesion or nine T2 MRI brain lesions
- ▶ one or more infratentorial lesions
- ▶ one or more juxtacortical lesions
- ▶ three or more periventricular lesions (a spinal cord lesion can replace some of these brain lesions).

Primary progressive MS may be diagnosed after 1 year of a progressive deficit and two of: plaques on a brain MR scan; plaques on a spinal cord MR scan; and unmatched CSF oligoclonal bands.

#### Optic neuritis

- ▶ First, patients experience unpleasant gritty eye pain, especially on eye movement. A day or two later they develop a central “smudge” in the vision of one eye, which progresses variably.
- ▶ The two key things to look for are a relative afferent pupillary defect at presentation, and clear recovery of vision. If there was no afferent pupillary defect, consider ocular causes of impaired vision (glaucoma, retinal detachment and central serous retinopathy).
- ▶ If visual acuity remains unimproved or is worsening, then imaging (eg, CT orbits) for a compressive optic neuropathy is mandatory, followed—if normal—by screening for vasculitis (giant cell arteritis in the right age group), viral infection and neuromyelitis optica.
- ▶ Bilateral optic neuritis or registered visual impairment are very rare in MS and raise other possibilities (see below).

#### Paroxysmal symptoms

The commonest structural cause of trigeminal neuralgia in young adults is MS. Other paroxysmal symptoms are much rarer and are pathognomonic of MS: brief (seconds–minutes) and very frequent (50–100/day) attacks of dysarthria/ataxia or unilateral dystonia, responding dramatically to carbamazepine.

#### “Rubral tremor”

Patients with advanced disability from MS often have signs of brainstem dysfunction with a

complex ophthalmoplegia, ataxia, head titubation, dysarthria and a sinuous tremor of the outstretched arm and hand.

#### The “useless hand”

(eponomously tagged the Oppenheim hand) is loss of proprioception but not strength or cutaneous sensation due to a plaque in the dorsal columns.

#### Cortical and cognitive syndromes

Dementia, epilepsy and focal deficits such as aphasia do occur, but are sufficiently rare to mandate the search for non-MS causes (see below).

#### Investigations

It is possible to diagnose MS without any investigations, but it would be unusual not to request *MR imaging* which is useful in various ways:

- ▶ Brain MRI demonstrates the white matter plaques of MS; particularly characteristic are lesions in the middle cerebellar peduncle, oval plaques orientated perpendicular to the lateral ventricles, and “mouse bites” in the corpus callosum. A single scan can demonstrate dissemination of lesions in space.
- ▶ Serial MR scans can be used to show dissemination of lesions in time which may substitute for clinical episodes under the McDonald criteria (see box). A gadolinium enhancing lesion on MRI represents active inflammation breaking down the blood-brain-barrier. A plaque is enhancing for about one month.
- ▶ Lesions of MS in the spinal cord are typically oval, less than three vertebral segments in length and affect only part of its axial cross-section. The cord lesions of neuromyelitis optica (see below) usually stretch for many vertebral segments and can affect the whole axial cross-section.
- ▶ Over the age of 50, non-specific white-matter lesions become common on MR brain scans and must not be confused with plaques. Spinal cord lesions retain their significance.

*Visual evoked potentials* is the only test that demonstrates demyelination in the optic nerve in patients with no evidence of previous optic neuropathy; the finding of abnormally delayed potentials may demonstrate dissemination in space.

*Cerebrospinal fluid (CSF) examination.* Oligoclonal immunoglobulin bands in the CSF, unmatched or in greater concentration than in serum, are found in 95% of people with MS. However, if the clinical history and MR brain scan are characteristic there is seldom any need for a lumbar puncture. It may be useful when there is diagnostic uncertainty such as in primary progressive MS, or in patients over the age of 50 with

**Table 1** The differential diagnosis of multiple sclerosis

Time course	Clinical features	Diagnosis	Notes
Monophasic illness	Cerebrum, optic nerve, cord, meningism, fever + epilepsy, death possible	Acute disseminated encephalomyelitis (ADEM)	Follows infection or vaccination
	Behaves like a space-occupying lesion	Tumefactive MS	This is often associated with anti-aquaporin-4 antibodies and so may be considered a form of "neuromyelitis optica". But tumefactive lesions may also be seen in otherwise normal MS
Relapsing-remitting illness	Cerebrum, optic nerve unusual, death possible	Toxic demyelination	Due to toxins in inhaled heroin ("chasing the dragon") or cocaine
	Optic nerve and spinal cord	Neuromyelitis optica (Devic's)	Anti-aquaporin-4 positive. Long spinal cord lesions
	Focal lesions, stroke like, headache, fever, skin rash	Vasculitis, either as part of a systemic disease or isolated to the CNS (which is very rare)	
	Cerebral + migraine + dementia	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Although imaging mimics MS in that corpus callosum may be involved, white matter lesions of temporal pole are very characteristic of CADASIL and never seen in MS. No oligoclonal bands in CSF
	Bilateral optic atrophy + typical MS syndromes + mitochondrial inheritance	Leber's hereditary optic neuropathy	Women with Leber's mitochondrial mutations may develop an MS-like illness
	Multifocal: cerebral and brainstem Limbs only	Stroke, especially due to small vessel disease Mononeuropathies from hereditary liability to pressure palsies	MRI cord and CSF may discriminate Physical signs and pattern of weakness should give the diagnosis
Progressive illness	Spinal cord and brainstem	Spinocerebellar ataxias	Family history. Imaging normal
	Spinal cord	Hereditary spastic paraparesis	Family history. Imaging usually normal
	Early dementia or epilepsy or peripheral neuropathy	A leukodystrophy	Characteristic imaging abnormalities. Look out for Addison's in men (adrenoleukodystrophy)

non-specific MRI white-matter lesions and a clinically suggestive history.

### PREDICTING PROGNOSIS IN MS

There is no reliable guide at the onset of MS to the likelihood of it causing greater or lesser disability. Vague indicators are that fixed disability is reached quicker by men, older patients, those with primary progressive disease and those who present with brainstem or cerebellar symptoms. In practice, neurologists tend to judge how aggressive the disease is by relapse frequency and the rate of new MRI lesion formation. However, these are surprisingly unhelpful. For instance, there is a correlation between the change in MRI lesion load over 5 years with MS and the disability of that individual 14 years later, but the correlation coefficient is only 0.6.

### THE DIFFERENTIAL DIAGNOSIS OF MS (TABLE 1)

Multiple sclerosis continues to be misdiagnosed. People with MS may first receive other diagnoses, often orthopaedic in men and psychiatric in women, before the penny drops. Conversely, non-organic symptoms may be wrongly attributed to MS.

**Neuromyelitis optica (NMO)** is the most common form of demyelinating disease in the Far East and Africa. Patients typically have monophasic or recurrent episodes of spinal cord and bilateral optic nerve syndromes, usually much more severe than in MS. Most, but not all, have serum antibodies to the water channel, aquaporin-4 and half of patients have other autoantibodies (anti-phospholipid and Sjögren's antibodies especially) which are probably epiphenomena of B cell dysregulation; this explains demyelination apparently

associated with systemic lupus erythematosus ("lupus sclerosis"), the antiphospholipid syndrome or other autoimmune disease. These patients have in fact NMO with non-pathogenic antibodies. MRI shows long spinal cord lesions (>3 vertebral segments in length) and symmetrical lesions ascending the white matter tracts from the brainstem, around the central canal, into the thalami. Cerebral lesions, if they occur, are usually large, oedematous and space-occupying, often being mistaken for glioma. Roughly 50% of attacks (which are usually unresponsive to steroids) may improve dramatically with plasma exchange. Long-term therapy is aimed at suppressing B cells and antibody formation (eg, prednisolone, azathioprine, rituximab).

**Acute disseminated encephalomyelitis (ADEM)** is a monophasic demyelinating disease in children and adults. As well as focal involvement of brainstem, both optic nerves and cord, patients characteristically have fever, meningism, seizures and reduced awareness. Death may occur due to gross cerebral oedema. ADEM is considered to be the consequence of a rare aberrant immune response to infections (viruses, mycoplasma, borrelia, campylobacter) or vaccinations. The brain MRI may be indistinguishable from MS but the lesions are said to more often involve the basal ganglia and cortex. CSF oligoclonal bands may be present, but less frequently than in MS, and they may not persist over time. There may be striking clinical and radiological improvement over weeks and months. Perhaps as many as 30% of typical episodes of ADEM may be followed by attacks which lead to the diagnosis of MS. Some claim there is an entity of "relapsing ADEM" which is distinguishable from MS.

**THE QUESTIONS PEOPLE WITH MS ASK**

It has to be remembered that the natural history data come largely from the era of poor support services and no disease-modifying drugs. However, there is no evidence yet that these treatments have any long-term effect.

**How is MS going to affect my life?**

- ▶ 50% need a stick to walk 20 years after the first symptoms.
- ▶ Half of all people with MS eventually have cognitive problems.
- ▶ Depression is three times more common and the suicide risk is doubled
- ▶ The divorce rate is increased ninefold.
- ▶ At least 2/3 of people with MS are unemployed (or 50% will become unemployed within 5 years of diagnosis).

**Am I going to die from MS?**

- ▶ Life expectancy is reduced by 10–15 years.
- ▶ It is very rare to die directly of MS (for instance respiratory failure from a high cervical plaque). However 2/3 of patients will die of secondary infections—particularly of skin, chest and bladder—due to advanced neurological disability.

**Will my children (or sibling) get MS?**

- ▶ The lifetime risk of MS in white northern Europeans is 0.3%.
- ▶ This increases to 25% for an identical twin of an MS patient, 5% for other siblings, 2% for a child, 1% in second or third-degree relatives.

**Can I have children?**

- ▶ MS does not affect fertility or pregnancy.
- ▶ During pregnancy the relapse rate is reduced, to be followed by an increased rate afterwards (though only 30% will relapse in the post-partum year) leading to no net change, but the perception among many women is that they are “at risk” after delivery.
- ▶ Epidural and spinal anaesthesia is safe.
- ▶ Breast feeding does not affect MS.
- ▶ For some people, an important factor is uncertainty over how future disability might affect their ability to look after any children.

**Should I go on a special diet?**

- ▶ Many unpleasant unproven diets have been and still are recommended.
- ▶ The NICE (National Institute for Health and Clinical Excellence) guidelines endorse poor-quality old studies which suggest that accumulation of disability can be reduced by diets rich in linoleic acid (sunflower, corn, soya and safflower oils). It is therefore reasonable to

recommend a healthy/Mediterranean diet, not least because this empowers patients.

**Can I have surgery?**

- ▶ General surgery and all types of anaesthesia are safe.
- ▶ There is histological evidence that plaques may form in the tracts caused by instrumentation of the brain or spinal cord.
- ▶ Myelography, which is very rarely needed nowadays, is considered safe.

**Should I have a vaccination?**

- ▶ Vaccinations do not cause or exacerbate MS.
- ▶ People with persistent disability should be offered influenza vaccination.

**Does stress cause MS or induce relapses?**

- ▶ Self-reported stressful life events double the risk of a relapse, but do not cause MS itself.

**Does smoking affect MS?**

- ▶ Smoking (or personality factors associated with smoking) increases the likelihood of conversion from relapsing-remitting MS to secondary progression.

**Does going on holiday to hot countries make MS worse?**

- ▶ No, this misunderstanding of the Uhthoff phenomenon (see above) is quite common.

**MANAGEMENT OF A RELAPSE**

If there is a question over acute treatment, or relapses are being counted as part of the criteria for possible disease-modifying therapies and in trials of new therapies, diagnosing a relapse correctly becomes very important. It is not always easy and not every patient can be relied upon to correctly diagnose their own relapses. When patients describe characteristic symptoms of demyelination (such as optic neuritis or myelopathy), it is possible for a neurologist or MS specialist nurse to diagnose a relapse over the telephone. If the patients have seen another doctor, who has found new objective clinical signs, the diagnosis of a relapse is reinforced. But it is generally best for the patient to have ready access to an MS centre providing “relapse clinics” which have been set up in several parts of the UK. Note:

- ▶ Consider alternative diagnoses if persistent deficits, eg if someone remains compromised from a myelopathy, consider spinal cord imaging for structural lesions (such as cervical spondylosis). “Optic neuritis” which has not recovered is particularly worrying (see above).

- ▶ Consider an underlying infection.
- ▶ Pyrexia, typically from a urinary tract infection may cause a Uhthoff mimic of a relapse (“pseudo-relapse”).
- ▶ Should the patient rest or exercise is an old question which remains unresolved.
- ▶ The NICE guidelines promote rapid access for people with a relapse to a dedicated rehabilitation unit.

### Corticosteroid treatment

- ▶ Corticosteroids reduce the duration of a relapse by a few weeks but have no effect on the disability accrued as a result of the attack eight weeks later, and have no impact on subsequent disease course; they should only be given for unpleasant or disabling symptoms and it may be reasonable to wait for a few days to see if there is spontaneous improvement.
- ▶ Oral or iv steroids, at home or in hospital, are probably equally effective, the standard regime in the UK is oral or iv methylprednisolone, 500 mg–1 g daily, for between 3 and 5 days.
- ▶ Common adverse effects are a metallic taste during the treatment and a few days of increased energy and insomnia. Aseptic necrosis of the hip

is a rare complication and—partly to prevent this—standard practice is to avoid giving more than three courses of corticosteroids in a year.

### Plasma exchange

There is some evidence that plasma exchange may improve 50% of steroid-resistant attacks of CNS demyelination, including relapses of MS and neuromyelitis optica.

### MANAGEMENT OF COMMON SYMPTOMS AND THE ANNUAL ASSESSMENT OF SOMEONE WITH MS

At different stages in the disease, various specialities become important to MS care, including urologists, ophthalmologists, speech and language therapists, physiotherapists, occupational therapists, clinical psychologists, psychiatrists, rehabilitation physicians and gastroenterologists. Coordination of these services has been revolutionised by the advent of the MS specialist professional (usually but not necessarily a nurse) who also liaises with social services, housing departments, wheelchair clinics, as well as providing continuity of care and pastoral support.

### Annual assessment

Best practice is that everyone with MS has the opportunity to see someone with specialist knowledge of their condition at least once a year. There is considerable benefit in doing such assessments in a multidisciplinary setting, with easy “one-stop” access to all the relevant professionals. The tasks during these assessments are to:

- ▶ briefly review the diagnosis
- ▶ define the stage of the disease
- ▶ record disability in some way, ideally using the Kurtzke scale (table 2)
- ▶ assess how many relapses there have been (for those in the relapsing-remitting phase, this may determine disease-modifying treatments)
- ▶ review persistent symptoms and their treatment (table 3).

Patients and their carers and relatives should be routinely asked about embarrassing or difficult symptoms such as depression, cognitive impairments, bladder and sexual problems (these are less likely to be volunteered by patients).

### CARE OF PEOPLE WITH ADVANCED MS

See table 3. Two initiatives have transformed the care of people with terminal neurological disability:

- ▶ greater willingness to use and accept advance directives
- ▶ greater involvement by palliative care services.

### DISEASE-MODIFYING THERAPIES

In 1993, the first trial was published of any drug to affect the course of MS: interferon-beta-1b reduced

**Table 2** Kurtzke Expanded Disability Severity Scale (EDSS). Despite its name, the EDSS is not a scale of disability alone; but of impairment (scores 0–3.5), disability (4.0–7.5) and handicap (8.0–10). It is an ordinal scale.

Score	Description
0.0	Normal neurological examination
1.0	No disability, minimal signs in one functional system (FS)*
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 h/day despite relatively severe disability; able to walk without aid or rest some 500 m
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk without aid or rest some 300 m.
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (stick, crutch, brace) required to walk about 100 metres with or without resting
6.5	Constant bilateral assistance (stick, crutches, braces) required to walk about 20 m without resting
7.0	Unable to walk beyond approximately five metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 h/day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms, retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

\*Each system (visual, pyramidal, etc) has a separate functional system scale which is scored and these scores are compiled to assist designation of the overall score.

**Table 3** Treatment of common symptoms of multiple sclerosis (MS) listed in order of efficacy of treatment (most useful first)

Symptom	First consider	Non-drug treatment	First-line treatment	Second-line treatment
Bladder—urgency or urge incontinence	Is there a urinary tract infection? Is the patient deliberately fluid restricting? Measure post-micturition residual bladder volume by ultrasound. Specialist continence advice	Intermittent self-catheterisation if the post-micturition residual bladder volume >100 ml	Oxybutinin (5 mg bd-qds), commonly causes dry mouth, constipation. Tolterodine (2 mg bd), rarely causes chest pain and peripheral oedema	Intravesical botulinum toxin in centres with experience. Long-term catheterisation only suitable if non-invasive methods do not work, and then suprapubic is better than in-dwelling. Do not use bladder wash-outs
Bladder—nocturia	Specialist continence advice	Specialist continence advice	Desmopressin 100–400 µg orally or 10–40 µg intranasally (for nocturia). Adverse effects are rare with correct dose: fluid retention, hyponatraemia	
Bladder—recurrent urinary tract infections (>3 in one year)	Always check culture and sensitivity, avoid long-term antibiotics. Consider bladder stones	Specialist continence advice		
Neuropathic pain	Carbamazepine specifically for trigeminal neuralgia. Consider musculoskeletal causes of pain, especially back pain secondary to spasticity	TENS, cognitive behaviour therapy	Amitriptyline, gabapentin, pregabalin	Lamotrigine, phenytoin
Hypersomnolence (rare)	Obstructive sleep apnoea		Modafanil (100–200 mg bd), adverse effects common: abdominal pain and diarrhoea	
Spasticity	Check for pain and infections (especially bladder). Careful check for contractures	Physiotherapy, passive stretching,	Baclofen (10 increasing to 80 mg daily in 2–3 divided doses) Tizanidine (starting at 2 mg, increasing by 2 mg every 3 days until on 4 mg tds and increase if still reporting benefit, to maximum of 24 mg daily Adverse effects: drowsiness, dizziness, dry mouth	Diazepam, clonazepam, dantrolene Intrathecal baclofen If limb function is already lost, then destructive surgery or phenol ablation of nerve roots In focal spasticity (eg hip adductors) botulinum toxin to paralyse appropriate muscles
Spastic foot drop		Functional electrical stimulator		
Constipation	Diet sufficient? Is hydration a problem? Can mobility be improved?	Increase fluid intake. Change diet	Oral laxatives	Suppositories and enemas
Depression	Consider social factors, eg isolation and loss of status, as well as a direct manifestation of the MS.	Support services (clinical psychology)	Antidepressant medication	
Dysphagia	Measure weight, formal swallow assessment, beware recurrent silent chest infections	Swallowing techniques, change in diet		Adjust position of seating, chest physiotherapy, enteral tube feeding
Chest infections	If recurrent, get formal swallow assessment			Enteral tube feeding
Dysarthria	Speech therapy			
Erectile dysfunction	Beware depression, diabetes, vascular disease and medications		Sildenafil 25–100 mg. Adverse effects: flushing, gastrointestinal disturbance, oedema	Alprostadil or intra-cavernosal papaverine
Pressure ulcers	Check nutrition and wheelchair fitting			
Faecal incontinence	Is this overflow from constipation? May need an abdominal x ray	Specialist continence advice	Oxybutinin or tolterodine may help	
Fatigue	Depression, poor sleep, sedating drugs	Energy-conservation techniques	Amantadine 200 mg bd (marginal efficacy). Adverse effects: anorexia, anxiety	Fluoxetine
Poor mobility	Is it all due to MS?	Aerobic training, rehabilitation, mobility aids		
Diplopia and oscillopsia			Gabapentin or baclofen may help	
Poor cognition	Assess formally and early. May be due to depression	Cognitive fatigue may improve with frequent rests (every 30 min) during high-performance mental tasks		
Emotionalism	Explain the condition to family and friends		Tricyclic antidepressant, selective serotonin reuptake inhibitor	
Ataxia and tremor		Specialist rehabilitation advice	A wide variety of proposed drugs (baclofen, isoniazid, carbamazepine, beta-blockers) have little or no effect	Thalamotomy and/or deep brain stimulation

**Table 4** Licensed disease-modifying drugs in the European Union and/or USA

Drug	Name	Administration	Adverse effects
Interferon-beta 1b	Betaferon or Betaseron	250 µg subcutaneously on alternate days	Local injection-site reactions and flu-like symptoms with pyrexia, which may be reduced by paracetamol and usually subside over months; abnormal liver function;
Interferon-beta 1a	Rebif	44 µg subcutaneous three times weekly	bone marrow suppression; 5–30% of patients develop persistent neutralising antibodies (higher with more frequent dosing) which may reduce efficacy
Interferon-beta 1a	Avonex	30 µg intramuscular once weekly	
Glatiramer acetate	Copaxone	30 µg subcutaneously daily	Injection site reactions; rarely a syndrome of severe pain at injection site +/- chest pain, which can occur months after starting drug
Natalizumab	Tysabri	300 mg by intravenous infusion every 4 weeks	Progressive multifocal leucoencephalopathy (?1/5000)—current licence refers to 1:1000
Mitoxantrone	Novantrone	Complex and various infusion regimes	Acute leukaemia (3/1000); cardiotoxicity (1:200)

the relapse rate by one third. Since then, we have learnt that several drugs (table 4) reduce the relapse rate and the accumulation of disability over the short term, 2–5 years; and that the outcome is better if drugs are given earlier in the course of the disease, and before significantly fixed disability is established. However, the long-term efficacy of these drugs is unclear. In particular, it is not known whether any influence the onset of the secondary progressive phase of the disease.

#### Treatment of the clinically isolated syndrome of demyelination

In people with white matter lesions on MR scans at presentation, the interferons and glatiramer acetate reduce the conversion to MS over the subsequent 3 years from about 50% to about 30%. It is currently unclear whether this translates into a significant effect on the accumulation of disability. Practice varies widely across Europe and the USA. However, in the UK, the considerable cost of these drugs, their debated efficacy and the

uncertain prognosis of MS has led to resistance to treating patients at this early stage.

#### Treatment of relapsing-remitting MS

The interferons and glatiramer acetate unequivocally reduce the relapse rate by about one third in the short term (fig 2). In pivotal trials, they also reduced the risk of acquiring fixed disability over 2 years from 38% to 28% although these results were not all statistically significant. A meta-analysis suggests that the interferons reduce the risk of relapse in the first year of treatment, but may have no effect on relapse rate after that, and they may have no impact on disability at all. The Association of British Neurologists (ABN) guidelines are that all eligible patients should be ambulant (maximum EDSS 6.5) and have one or more indicator of disease activity out of: two “clinically significant” relapses in the last two years; one “disabling” relapse in the last year; an active MR scan containing new or gadolinium enhancing lesions that have developed in the previous year.

#### Treatment of the secondary progressive phase MS

The interferons and glatiramer acetate do not affect secondary progression, and there is an increasing perception that no immunotherapy, however potent, will.

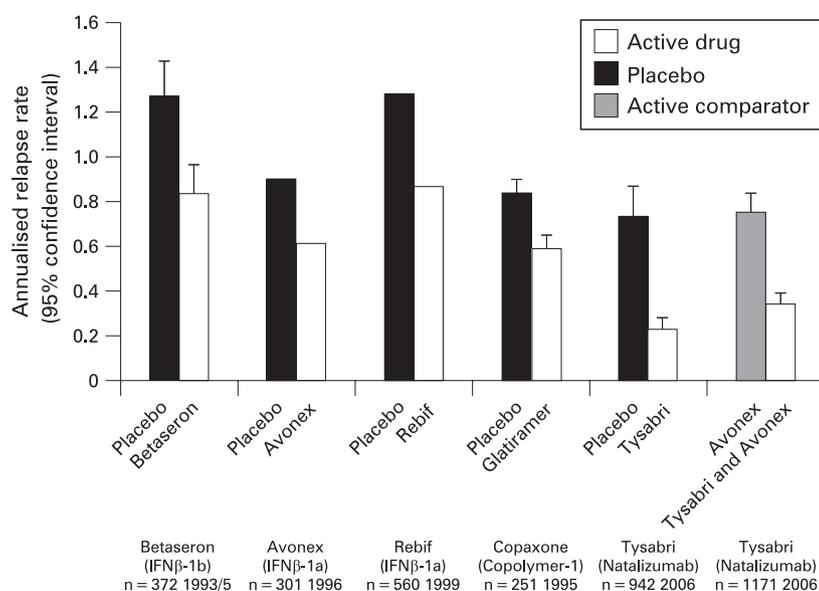
#### Treatment of primary progressive phase MS

There is no effective disease modifying drug.

#### Stopping interferon-beta or glatiramer acetate

It is very difficult to stop disease-modifying treatment in an individual patient (“But you don’t know what my relapse rate would have been without treatment, doctor”). The ABN has suggested these stopping criteria:

- ▶ increased number and severity of relapses or lack of relapse reduction compared with the pre-treatment 1–2 years, especially if MRI shows new or enhancing lesions
- ▶ development of non-relapsing secondary progressive multiple sclerosis, with loss of the ability to walk (EDSS 7 or more).



**Figure 2** The annualised relapse rate from the pivotal trials of the interferons and copaxone. There are no error bars for columns 2 and 3 as not all of the papers summarised contained the standard deviation of the data.

## Further reading

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The role of testing for neutralising antibodies to interferon-beta is unclear. One approach, advocated by European authorities, is to systematically test everyone annually and offer those with high concentration antibodies an alternative treatment such as glatiramer acetate.

**Treatment of aggressive relapsing-remitting MS**

People who continue to relapse on interferon-beta or glatiramer acetate, or who present so aggressively that the neurologist has little faith in interferon-beta's ability to contain the disease, may be considered for natalizumab or mitoxantrone. Both should be given in a regional MS centre.

- ▶ Natalizumab, given indefinitely by monthly infusion, is very roughly twice as efficacious as interferon-beta, reducing the relapse rate at 1 year by 68% and the chance of acquiring fixed disability over 2 years by 42% compared to placebo. The main concern is a low risk (yet to be established, but perhaps 1/5000) of progressive multifocal leucoencephalopathy. The annual cost is around £20,000, roughly double that of the interferons.
- ▶ Mitoxantrone is licensed for the treatment of "worsening relapsing MS" (which means either aggressive relapsing-remitting disease or progressive MS with frequent superimposed relapses) in the USA, but is unlicensed in Europe. It is a cheap chemotherapy (cytotoxic

immunosuppressant) drug, which may be as effective, or more, than natalizumab, but also has significant adverse effects: total dose exposure is limited by cardiotoxicity and 0.2% risk of acute leukaemia. It is useful as short-term "rescue" treatment for at most 3 years. It may perhaps be better used as induction therapy allowing patients to be maintained long term on less noxious drugs, though the evidence for this approach is limited.

**Future treatment of MS**

Over the next few years, neurologists will have to come to terms with a wide variety of drugs for the treatment of MS, especially new biologicals. Currently under investigation are novel monoclonal antibodies; oral immunotherapies; combination immunotherapies; peptide vaccination; neuroprotective drugs; and reparative strategies using stem cells. Perhaps more significantly there is growing evidence that the benefits of aggressive immunotherapy are greatest when given earliest in the course of the disease. This raises the difficult prospect of exposing well non-disabled young adults to potentially toxic treatments, which would be much easier if there were good prognostic indicators early in the disease.

**CONCLUSIONS**

- ▶ MS is an inflammatory demyelinating disorder of the CNS in which there is dissemination of lesions in time and space.
- ▶ MS is the commonest cause of neurological disability in young adults in the West.
- ▶ The diagnosis is usually clinical, supported by MRI. New criteria, largely for research, allow for new asymptomatic radiological lesions to replace the need for a second clinical episode in making the diagnosis of MS.
- ▶ MR scans may also inform prognosis: for instance, abnormalities at the time of a first episode of demyelination increase the risk of developing MS.
- ▶ An important differential is neuromyelitis optica, characterised by long spinal cord lesions, bilateral optic neuropathy and sometimes antibodies against aquaporin-4.
- ▶ Useful quality of life improvements come from specialist nurses co-ordinating multidisciplinary care of MS patients.
- ▶ Corticosteroids reduce the duration, but not the eventual outcome, of acute episodes of MS.
- ▶ Current trends in disease-modifying treatments are (i) to treat earlier in the disease course and (ii) to use more aggressive immunotherapies with greater toxicity.

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